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EXAMINER	
ORWIG, KEVIN S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,614	SUBR ET AL.	
	Examiner	Art Unit	
	Kevin S. Orwig	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-12* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-8 and 10-12 are currently pending. Claims 1-8 are the subject of this Office Action. This is the first Office Action on the merits of the claims. Non-elected claims 10-12 are withdrawn from consideration.

Election/Restrictions

Applicant's election of Group I (claims 1-8) in the reply filed on Aug. 12, 2008 is acknowledged. In response to applicant's election, Group II (claims 10-12) is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 9 and 13-16 have been cancelled. Applicants have elected Group I with traverse.

The traversal is on the ground(s) that the method claims (i.e. Group II) describe a method for polymer preparation which further limits claim 1 and that the art cited to break unity (i.e. International Patent Application Publication No. WO 99/30727; Published Jun. 24, 1999; hereinafter Greenwald *et al.*) does not anticipate or render obvious the instantly claimed invention. This traversal is not found to be persuasive because there are two inventions, one drawn to a polymer, and one drawn to a method. Group I is drawn to a different statutory category of invention (a composition of matter) than Group II, which is drawn to a method. While related by the claimed polymer, the two inventions are not so closely related as to depend absolutely upon one another and are therefore patentably distinct.

Applicants assert that Greenwald *et al.* does not anticipate or render obvious the instantly claimed invention because the exemplified polymers only based on polyethylene glycol (PEG). While the disclosure of Greenwald *et al.* is drawn predominantly to PEG (and derivatives thereof) as a polymer core, other cores, including HMPA are clearly taught as well. As pointed out in the restriction requirement of Jul. 18, 2008, Greenwald *et al.* disclose polymeric prodrugs wherein the polymeric transport cores may be based on hydroxypropylmethacrylamide (HPMA) (page 17, lines 6-10). It is noted that HPMA is commonly regarded in the art as having the hydroxyl group at the 2 position of the propyl chain, and HPMA as taught by Greenwald *et al.* denotes a homopolymeric (i.e. having approximately 100% of the monomer units of N-(2-hydroxypropyl)methacrylamide) structure, as would be apparent to one of ordinary skill in the art. The termini of these polymers may be activated with thiazolidine-2-thione groups as taught by Greenwald *et al.* (examples 1, 5, 8, and 10; figures 2, 3, and 5), reading on the reactive polymers/copolymers of instant claim 1. Thus, the restriction requirement is still deemed proper and is therefore made FINAL.

Priority

The earliest effective U.S. filing date afforded the instantly claimed invention has been determined to be Jul. 15, 2004, the filing date of PCT application PCT/IB04/52127 to which the instant national stage 371 application claims priority. Acknowledgment is made of applicant's claim to foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of the Czech application was filed with the USPTO on Sep 24, 2004.

Information Disclosure Statement

No Information Disclosure Statements have been filed with the present application. Applicants are reminded of their duty to disclose patents and publications relevant to the patentability of the instant claims.

Abstract

The abstract of the disclosure is objected to because the language of the abstract is atypical for U.S. national stage applications. Specifically, the phrase "the solution" is more proper in international stage applications, and should be changed to "the invention" or the like in order to conform to common U.S. terminology standards and improve clarity and readability. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 1 is objected to because of the following informalities: the phrase "based on" is imprecise and extremely broad. This phrase should replaced with more appropriate language such as "comprising" or an equivalent term to indicate the

inclusion of N-(2-hydroxypropyl)methacrylamide and not a vague relationship to this constituent.

Claim 1 is objected to because of the following informalities: the word "N-(2-hydroxypropyl)methacrylamid" should be "N-(2-hydroxypropyl)methacrylamide".

Claim 1 is objected to because of the following informalities: the article "a" should be inserted between the words "either" and "component".

Claim 1 is objected to because of the following informalities: the article "the" should be inserted between the words "through" and "nitrogen".

Claim 3 is objected to because of the following informalities: the article "the" should be inserted between the words "of" and "polymer".

Claim 4 is objected to because of the following informalities: the word "consist" in line 4 of the claim should be "consisting".

Claim 5 is objected to because of the following informalities: the word "grouping" in line 4 of the claim should be "group".

Claim 5 is objected to because of the following informalities: the article "a" should be inserted between the word "bearing" and the following parentheses.

Claim 7 is objected to because of the following informalities: the article "a" should be inserted between the word "bearing" and the following parentheses.

Claim 12 is objected to because of the following informalities: the word "doxorubicine" should be " doxorubicin".

Appropriate correction is required.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "oligopeptides of doxorubicin" is unclear since peptides of doxorubicin do not exist and it is unclear what is meant by this phrase. This term is not defined by the claims, the specification does not provide a sufficient standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The examiner suggests changing this phrase to "oligopeptides conjugated to doxorubicin" or similar language to clarify this phrase.

Claims 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites polymers containing from 0.1-5% monomer units of N-methacryloylated oligopeptides. It is apparent from the instant specification (Figures 5-7) that such modified N-methacryloylated monomers are not N-(2-hydroxypropyl)methacrylamides. Since claim 6 depends from claim 5, which recites 100% N-(2-hydroxypropyl)methacrylamide monomers, it is not possible to also have from 0.1-5% monomer units of N-methacryloylated oligopeptides in these same polymers.

Likewise, claim 8 recites polymers containing from 0.1-5% monomer units of N-methacryloylated oligopeptides. Since claim 8 depends from claim 7, which recites 100% N-(2-hydroxypropyl)methacrylamide monomers, it is not possible to also have

from 0.1-5% monomer units of N-methacryloylated oligopeptides in these same polymers. Thus, claims 6 and 8 are indefinite.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Greenwald *et al.* (International Publication No. WO 99/30727; Published Jun. 24, 1999) (hereinafter Greenwald *et al.*) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Greenwald *et al* as evidenced by Ulbrich *et al.* (K. Ulbrich *et al.*, J. Controlled Release (2000) 64, p. 63-79) (hereinafter Ulbrich *et al.*).

1. Greenwald *et al.* disclose prodrugs based on polymeric transport cores (abstract). Greenwald *et al.* teach the use of a variety of polymers as the basis of their invention including, inter alia, hydroxypropylmethacrylamide (HPMA) and copolymers thereof (page 17, lines 6-10). This teaching makes a distinction between a polymer of HPMA alone and copolymers of HPMA with other polymers. Thus, the HPMA as taught

by Greenwald *et al.* is a homopolymer in at least one embodiment, in which case approximately 100% (i.e. minimally 60%) of the monomer units are hydroxypropylmethacrylamide units. It is noted that conventional usage of the terms hydroxypropylmethacrylamide (HPMA) and polyhydroxypropylmethacrylamide (PHPMA) refer to the 2-hydroxypropyl form of the HPMA monomer (i.e. N-(2-hydroxypropyl)methacrylamide), as evidenced by Ulbrich *et al.* (page 64, left column, second paragraph; page 65, left column under heading 2.5 Synthesis of Monomers). Furthermore, Greenwald *et al.* teach the use of thiazolidine-2-thione groups bound through the nitrogen of the thiazolidine-2-thione group to a carbonyl group that is a component of a linker at the end of the polymer chain (page 5, lines 6-8; examples 1, 5, 8, and 10; figures 2, 3, and 5), reading on instant claims 1 and 3.

2. Alternatively, given the meaning of HPMA commonly used in the art (see Ulbrich *et al.* evidentiary reference) it would have been obvious to one of ordinary skill in the art at the time of the invention to use a homopolymer of N-(2-hydroxypropyl)methacrylamide (i.e. approximately 100% of N-(2-hydroxypropyl)methacrylamide groups) as the polymeric core in light of the disclosure of Greenwald *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulbrich *et al.* (K. Ulbrich *et al.*, J. Controlled Release (2000) 64, p. 63-79) (hereinafter Ulbrich *et al.*) in view of Greenwald *et al.* (R. B. Greenwald, Bioconjugate Chem. (1996) 7, p. 638-641) (hereinafter Greenwald(1996)).

4. Ulbrich *et al.* disclose the synthesis and characterization of poly(HPMA) conjugates with various therapeutic molecules, including proteins, antibodies, and anti-cancer drugs such as doxorubicin (abstract). These conjugates are based on N-(2-hydroxypropyl)methacrylamide (HPMA) (page 64, left column, 2nd paragraph) and contain more than 60% of the N-(2-hydroxypropyl)methacrylamide monomer (i.e. the monomer is in a 10:1 ratio with methacrylolyated *p*-nitrophenyl esters (page 66, right column, under heading 2.6 Synthesis of polymer precursors). Ulbrich *et al.* teach activation of the relevant carboxylic acid groups using succinimidyl esters (i.e. using H-

OSu) (page 66, bottom of right column; Figure 2, line), however Ulbrich *et al.* do not teach the use of thiazolidine-2-thione in this capacity.

5. Greenwald(1996) teach thiazolidine-2-thione as a reagent for protein modification that is particularly advantageous over traditional succinimidyl linkers (abstract; compounds 6 and 7). Greenwald(1996) teach that thiazolidine-2-thione is a superior modification reagent relative to its succinimidyl counterparts because it can be used under mild conditions with only minor pH fluctuations (eliminating problems with protein denaturation encountered with succinimide reagents) and is more stable (pages 640-641, discussion section). Greenwald(1996) additionally teach that, its advantages not withstanding, thiazolidine-2-thione is an otherwise equivalent reagent to the succinimide reagents (page 641, last paragraph of discussion section). In light of these teachings, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute thiazolidine-2-thione for the succinimide type reagents taught by Ulbrich *et al.* in order to obtain these advantageous properties. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to substitute thiazolidine-2-thione as a functional equivalent for succinimides and other activating reagents used by Ulbrich *et al.* per the teachings of Greenwald(1996), to obtain a more stable linker in the conjugates of Ulbrich *et al.*, reading on instant claim 1.

6. Regarding instant claims 2 and 3, Ulbrich *et al.* teach two types of conjugation (abstract). In the first type of conjugation the pendant molecules (e.g. proteins) are attached to the polymer via the side chain of the polymer backbone, and in the second

type of conjugation the pendant molecules are attached via the end-chain functional groups of the polymers (abstract), reading on instant claims 2 and 3.

7. Regarding claim 4, while Ulbrich *et al.* are silent as to the specific number of monomer units linked in the polymer chains of their invention, they teach that the conjugated polymer may have a molecular weight of 13,000 g/mol (Table 1). Taking, for example, entry 1 in Table 1, 8.2 mol% of the polymer is comprised of reactive monomer units consisting of N-methacryloylated (Ma) oligopeptides (in this case GlyPheLeuGly) containing reactive groups, leaving 91.8 mol% of the polymer that composed N-(2-hydroxypropyl)methacrylamide units. 91.8 mol% of 13,000 g/mol gives an effective molecular weight for the N-(2-hydroxypropyl)methacrylamide portion of the polymer of 11,934 g/mol. Since each N-(2-hydroxypropyl)methacrylamide residue has a molecular weight of approximately 143.2 g/mol, this corresponds to about 83 N-(2-hydroxypropyl)methacrylamide monomer units (11,934 g/mol divided by 143.2 g/mol). Thus, Ulbrich *et al.* teach each element of instant claim 4 except for the use of thiazolidine-2-thione as the reactive group. However, as discussed above, in light of the teachings of Greenwald(1996), substitution of thiazolidine-2-thione for the reactive groups taught by Ulbrich *et al.* is an obvious variation of this polymer conjugate. Thus, the combined teachings of Ulbrich *et al.* and Greenwald(1996) read on instant claim 4.

8. Regarding claim 5, Ulbrich *et al.* teach the use of 3-mercaptopropionic acid (MPA) (i.e. 3-sulfanylpropanoic acid) as a chain transfer agent used in conjunction with succinimide reagents (page 66, right column; Figure 2, polymer precursor structure IV). Substitution of thiazolidine-2-thione into the polymer conjugate system taught by Ulbrich

et al. would thus result in a (3-sulfanylpropanoyl)-thiazolidine-2-thione group, and is obvious by the reasoning applied above. Ulbrich *et al.* teach that the polymers of their study may have approximately 83 monomer units as discussed above. Furthermore, Ulbrich *et al.* teach that the content of the oligopeptide-doxorubicin monomers can be varied in the polymerization mixture. Based on this teaching, one of ordinary skill in the art would readily have envisioned varying the oligopeptide-doxorubicin monomer content by removing it completely, resulting in a polymer of 100% N-(2-hydroxypropyl)methacrylamide units.

9. Regarding claim 6, Ulbrich *et al.* teach N-methacryloylated oligopeptides containing doxorubicin where the oligopeptides may be, *inter alia*, GlyPheLeuGly (Figure 2; Table 1), but are silent as to the specific % of N-methacryloylated oligopeptides containing doxorubicin present in their polymer system. However, Ulbrich *et al.* teach that the content of doxorubicin can be varied by changing the content of the N-methacryloylated oligopeptides containing doxorubicin (thus changing the percentage of monomer units containing doxorubicin) in the polymerization mixture (page 67, left column, bottom of the page), as would be apparent to and well within the skill of one of ordinary skill in the art. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to vary the amount of the doxorubicin-containing oligopeptide monomers in the polymerization mixture per the teachings of Ulbrich *et al.*, to achieve a sufficient amount of doxorubicin in the final polymer conjugate, reading on instant claim 6.

10. Regarding claim 7, Ulbrich *et al.* teach the preparation of the polymer conjugates via radical precipitation copolymerization using 2,2'-azobisisobutyronitrile (AIBN), a well-known radical initiator, to begin the process of polymerization (page 64, right column; page 66, right column). Ulbrich *et al.* teach that the polymers of their study may have approximately 83 monomer units as discussed above. Furthermore, Ulbrich *et al.* teach that the content of the oligopeptide-doxorubicin monomers can be varied in the polymerization mixture. Based on this teaching, one of ordinary skill in the art would readily have envisioned varying the oligopeptide-doxorubicin monomer content by removing it completely, resulting in a polymer of 100% N-(2-hydroxypropyl)methacrylamide units. The substitution of thiazolidine-2-thione for the activating agents in the polymer conjugate system taught by Ulbrich *et al.* is obvious by the reasoning applied above. Since Ulbrich *et al.* teach the use of AIBN to initiate the radical polymerization, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use AIBN as the radical initiator in conjunction with thiazolidine-2-thione per the teachings of Greenwald(1996) to initiate the polymerization reaction. The combination of these reagents would result in a (4-cyanopentanoyl)-thiazolidine-2-thione group at the chain end, reading on instant claim 7.

11. Regarding claim 8, Ulbrich *et al.* teach N-methacryloylated oligopeptides containing doxorubicin where the oligopeptides may be, *inter alia*, GlyPheLeuGly (Figure 2; Table 1), but are silent as to the specific % of N-methacryloylated oligopeptides containing doxorubicin present in their polymer system. However, Ulbrich *et al.* teach that the content of doxorubicin can be varied by changing the content of the

N-methacryloylated oligopeptides containing doxorubicin (thus changing the percentage of monomer units containing doxorubicin) in the polymerization mixture (page 67, left column, bottom of the page), as would be apparent to and well within the skill of one of ordinary skill in the art. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to vary the amount of the doxorubicin-containing oligopeptide monomers in the polymerization mixture per the teachings of Ulbrich *et al.*, to achieve a sufficient amount of doxorubicin in the final polymer conjugate, reading on instant claim 8.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin S. Orwig whose telephone number is (571)270-5869. The examiner can normally be reached Monday-Friday 7:00 am-4:00 pm (with alternate Fridays off). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached Monday-Friday 8:00 am-5:00 pm at (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KSO

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4161